SiteMap 2.0

User Manual

Schrödinger Press

April 2006

Contents

Document Conventions

In addition to the use of italics for names of documents, the font conventions that are used in this document are summarized in the table below.

Table 2.1.

Font	Example	Use
Sans serif	Project Table	Names of GUI features, such as panels, menus, menu items, buttons, and labels
Monospace	`$SCHRODINGER/maestro`	File names, directory names, commands, environment variables, and screen output
Italic	*filename*	Text that the user must replace with a value
Sans serif uppercase	CTRL+H	Keyboard keys

In descriptions of command syntax, the following UNIX conventions are used: braces `{ }` enclose a choice of required items, square brackets `[ ]` enclose optional items, and the bar symbol | separates items in a list from which one item must be chosen. Lines of command syntax that wrap should be interpreted as a single command.

In this document, to *type* text means to type the required text in the specified location, and to *enter* text means to type the required text, then press the ENTER key.

References to literature sources are given in square brackets, like this: [10].

Introduction to SiteMap

1.1 SiteMap Overview

The location of the primary binding site on a receptor such as a protein is often known from the structure of a co-crystallized complex. Efforts to design better ligands for these receptors can profit from an understanding of how well the known ligands complement the receptor, and how extension of the ligands into adjacent regions could promote binding. Determining whether there are nearby sites that might be useful for allosteric binding can also be important.

In some cases, however, the location of a binding site for protein-ligand or protein-protein interactions is not known in advance, even though the protein structures are available. Here, computational studies can help to suggest likely binding sites, and even to predict whether a given protein is likely to bind ligands tightly. Many such approaches have been explored; for references, see the recent paper by Nayal and Honig [1].

SiteMap generates information on the character of binding sites using novel search and analysis facilities, and provides information to Maestro for visualization of the sites. A SiteMap calculation begins with an initial search stage that determines one or more regions on or near the protein surface, called *sites,* that may be suitable for binding of a ligand to the receptor. The search uses a grid of points, called *site points*, to locate the sites. In the second stage, contour maps (*site maps*) are generated, producing hydrophobic and hydrophilic maps. The hydrophilic maps are further divided into donor, acceptor, and metal-binding regions. The evaluation stage, which concludes the calculation, assesses each site by calculating various properties, which are added to the Maestro project.

Site maps can aid in the design of better ligands, by revealing "targets of opportunity"—for example, hydrophobic regions that have room to accommodate a larger hydrophobic group. Site maps can also be used to select the target for ligand docking with Glide and to evaluate docking hits, by showing the how well the poses display proper complementarity to the receptor. The regions that are neither hydrophobic nor hydrophilic are important because they show places in which it may be possible to improve the physical properties of the ligand—for example, by changing the solubility—with minimal effect on the binding affinity.

In contrast to techniques that color-code the receptor surface to represent hydrophilicity or hydrophobicity, site maps depend on the site as a whole, not just the character of the nearest receptor atom. Moreover, site maps explicitly show the shape and extent of philic and phobic regions, something a surface-based display cannot do.

The most important property generated by SiteMap is an overall SiteScore, which has proven to be effective at identifying known binding sites in co-crystallized complexes. Other properties characterize the binding site in terms of:

- the size of the site,
- the degrees of enclosure by the protein and exposure to solvent,
- the tightness with which the site points interact with the receptor,
- the hydrophobic and hydrophilic character of the site and the balance between them,
- the degree to which a ligand might donate or accept hydrogen bonds.

SiteMap can be run either from Maestro or from the command line. A SiteMap calculation typically takes a few minutes for proteins having up to 5000 atoms. Version 2.0 of SiteMap contains many improvements over the original SiteMap, which is still available from the Surfaces submenu of the Display menu in Maestro, as Hydrophobic/philic.

1.2 Citing SiteMap in Publications

The use of this program should be acknowledged in publications as:

SiteMap, version 2.0, Schrödinger, LLC, New York, NY, 2005.

Introduction to Maestro

Maestro is the graphical user interface for all of Schrödinger's products: CombiGlide™, Epik™, Glide™, Impact™, Jaguar™, Liaison™, LigPrep™, MacroModel®, Phase™, Prime™, QikProp™, QSite™, and Strike™. It contains tools for building, displaying, and manipulating chemical structures; for organizing, loading, and storing these structures and associated data; and for setting up, monitoring, and visualizing the results of calculations on these structures. This chapter provides a brief introduction to Maestro and some of its capabilities. For more information on any of the topics in this chapter, see the *Maestro User Manual*.

2.1 General Interface Behavior

Most Maestro panels are amodal: more than one panel can be open at a time, and a panel need not be closed for an action to be carried out. Each Maestro panel has a Close button so you can hide the panel from view.

Maestro supports the mouse functions common to many graphical user interfaces. The left button is used for choosing menu items, clicking buttons, and selecting objects by clicking or dragging. This button is also used for resizing and moving panels. The right button displays a shortcut menu. Other common mouse functions are supported, such as using the mouse in combination with the SHIFT or CTRL keys to select a range of items and select or deselect a single item without affecting other items.

In addition, the mouse buttons are used for special functions described later in this chapter. These functions assume that you have a three-button mouse. If you have a two-button mouse, ensure that it is configured for three-button mouse simulation (the middle mouse button is simulated by pressing or holding down both buttons simultaneously).

2.2 Starting Maestro

Before starting Maestro, you must first set the `SCHRODINGER` environment variable to point to the installation directory. To set this variable, enter the following command at a shell prompt:

csh/tcsh: `setenv SCHRODINGER` *installation-directory*

bash/ksh: `export SCHRODINGER=`*installation-directory*

You might also need to set the DISPLAY environment variable, if it is not set automatically when you log in. To determine if you need to set this variable, enter the command:

```
echo $DISPLAY
```

If the response is a blank line, set the variable by entering the following command:

csh/tcsh: `setenv DISPLAY` *display-machine-name*`:0.0`

bash/ksh: `export DISPLAY=`*display-machine-name*`:0.0`

After you set the SCHRODINGER and DISPLAY environment variables, you can start Maestro using the command:

```
$SCHRODINGER/maestro options
```

If you add the $SCHRODINGER directory to your path, you only need to enter the command maestro. Options for this command are given in Section 2.1 of the *Maestro User Manual*.

The directory from which you started Maestro is Maestro's current working directory, and all data files are written to and read from this directory unless otherwise specified (see Section 2.8 on page 25). You can change directories by entering the following command in the command input area (see page 6) of the main window:

```
cd directory-name
```

where *directory-name* is either a full path or a relative path.

2.3 The Maestro Main Window

The Maestro main window is shown in Figure 2.1 on page 5. The main window components are listed below.

The following components are always visible:

- **Title bar**—displays the Maestro version, the project name (if there is one) and the current working directory.
- **Auto-Help**—automatically displays context-sensitive help.
- **Menu bar**—provides access to panels.
- **Workspace**—displays molecular structures and other 3D graphical objects.

The following components can be displayed or hidden by choosing the component from the Display menu. Your choice of which main window components are displayed is persistent between Maestro sessions.

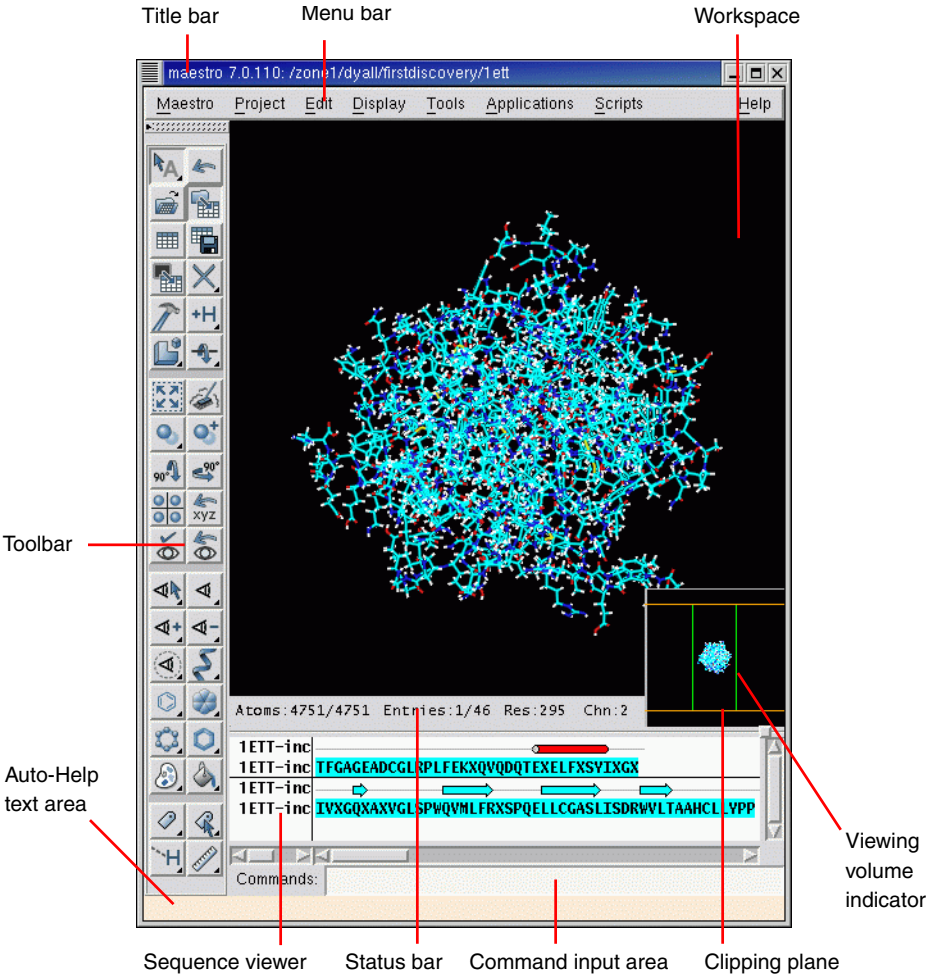

Figure 2.1. The Maestro main window.

- **Toolbar**—contains buttons for many common tasks and provides tools for displaying and manipulating structures, as well as organizing the Workspace.
- **Status bar**—displays information about a particular atom, or about structures in the Workspace, depending on where the pointer pauses (see Section 2.5 of the *Maestro User Manual* for details):
  - **Atom**—displays the chain, residue number, element, PDB atom name, formal charge, and title or entry name (this last field is set by choosing Preferences from the Maestro menu and selecting the Feedback folder).

  - **Workspace**—displays the number of atoms, entries, residues, chains, and molecules in the Workspace.

- **Clipping planes window**—displays a small, top view of the Workspace and shows the clipping planes and viewing volume indicators.
- **Sequence viewer**—shows the sequences for proteins displayed in the Workspace. See Section 2.6 of the *Maestro User Manual* for details.
- **Command input area**—provides a place to enter Maestro commands.

When a distinction between components in the main window and those in other panels is needed, the term *main* is applied to the main window components (e.g., main toolbar).

You can expand the Workspace to occupy the full screen, by pressing CTRL+=. All other components and panels are hidden. To return to the previous display, press CTRL+= again.

2.3.1 The Menu Bar

The menus on the main menu bar provide access to panels, allow you to execute commands, and control the appearance of the Workspace. The main menus are as follows:

- Maestro—save or print images in the Workspace, execute system commands, save or load a panel layout, set preferences, set up Maestro command aliases, and quit Maestro.
- Project—open and close projects, import and export structures, make a snapshot, and annotate a project. These actions can also be performed from the Project Table panel. For more information, see Section 2.4 on page 11.
- Edit—undo actions, build and modify structures, define command scripts and macros, and find atoms in the Workspace.
- Display—control the display of the contents of the Workspace, arrange panels, and display or hide main window components.
- Tools—group atoms; measure, align, and superimpose structures; and view and visualize data.
- Applications—set up, submit, and monitor jobs for Schrödinger's computational programs. Some products have a submenu from which you can choose the task to be performed.
- Scripts—manage and install Python scripts that come with the distribution and scripts that you create yourself. (See Chapter 13 of the *Maestro User Manual* for details.)
- Help—open the Help panel, the PDF documentation index, or information panels; run a demonstration; and display or hide Balloon Help (tooltips).

2.3.2 The Toolbar

The main toolbar contains three kinds of buttons for performing common tasks:

Action—Perform a simple task, like clearing the Workspace.

Display—Open or close a panel or open a dialog box, such as the Project Table panel.

Menu—Display a *button menu*. These buttons have a triangle in the lower right corner.

There are four types of items on button menus, and all four types can be on the same menu (see Figure 2.2):

- **Action**—Perform an action immediately.
- **Display**—Open a panel or dialog box.
- **Object types for selection**—Choose Atoms, Bonds, Residues, Chains, Molecules, or Entries, then click on an atom in the Workspace to perform the action on all the atoms in that structural unit.

  The object type is marked on the menu with a red diamond and the button is indented to indicate the action to be performed.
- **Other setting**—Set a state, choose an attribute, or choose a parameter and click on atoms in the Workspace to display or change that parameter.

The toolbar buttons are described below. Some descriptions refer to features not described in this chapter. See the *Maestro User Manual* for a fuller description of these features.

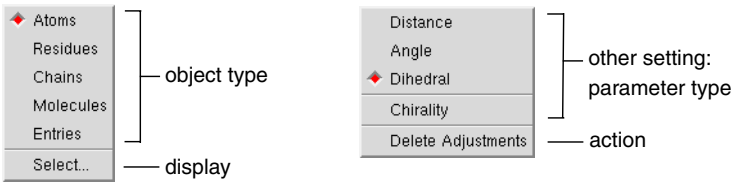

Figure 2.2. The Workspace selection ***button menu and the*** Adjust distances, angles or dihedrals ***button menu.***

Workspace selection
– Choose an object type for selecting
– Open the Atom Selection dialog box

Undo/Redo
Undo or redo the last action. Performs the same function as the Undo item on the Edit menu, and changes to an arrow pointing in the opposite direction when an Undo has been performed, indicating that its next action is Redo.

Open a project
Open the Open Project dialog box.

Import structures
Open the Import panel.

Open/Close Project Table
Open the Project Table panel or close it if it is open.

Save as
Open the Save Project As dialog box, to save the project with a new name.

Create entry from Workspace
Open a dialog box in which you can create an entry in the current project using the contents of the Workspace.

Delete
– Choose an object type for deletion
– Delete hydrogens and waters
– Open the Atom Selection dialog box
– Delete other items associated with the structures in the Workspace
– Click to select atoms to delete
– Double-click to delete all atoms

Open/Close Build panel
Open the Build panel or close it if it is open.

Add hydrogens
– Choose an object type for applying a hydrogen treatment
– Open the Atom Selection dialog box
– Click to select atoms to treat
– Double-click to apply to all atoms

Local transformation
– Choose an object type for transforming
– Click to select atoms to transform
– Open the Advanced Transformations panel

Adjust distances, angles or dihedrals
– Choose a parameter for adjusting
– Delete adjustments

Fit to screen
Scale the displayed structure to fit into the Workspace and reset the center of rotation.

Clear Workspace
Clear all atoms from the Workspace.

Set fog display state
Choose a fog state. Automatic means fog is on when there are more than 40 atoms in the Workspace, otherwise it is off.

Enhance depth cues
Optimize fogging and other depth cues based on what is in the Workspace.

Rotate around X axis by 90 degrees
Rotate the Workspace contents around the X axis by 90 degrees.

Rotate around Y axis by 90 degrees
Rotate the Workspace contents around the Y axis by 90 degrees.

Tile entries
Arrange entries in a rectangular grid in the Workspace.

Reset Workspace
Reset the rotation, translation, and zoom of the Workspace to the default state.

Save view
Save the current view of the Workspace: orientation, location, and zoom.

Restore view
Restore the last saved view of the Workspace: orientation, location, and zoom.

Display only selected atoms
– Choose an object type for displaying
– Click to select atoms to display
– Double-click to display all atoms

Display only
– Choose a predefined atom category
– Open the Atom Selection dialog box

Also display
– Choose a predefined atom category
– Open the Atom Selection dialog box

Undisplay
– Choose a predefined atom category
– Open the Atom Selection dialog box

Display residues within N angstroms of currently displayed atoms
– Choose a radius
– Open a dialog box to set a value

Show, hide, or color ribbons
– Choose to show or hide ribbons
– Choose a color scheme for coloring ribbons

Draw bonds in wire
– Choose an object type for drawing bonds in wire representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Draw atoms in CPK
– Choose an object type for drawing bonds in CPK representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Draw atoms in Ball & Stick
– Choose an object type for drawing bonds in Ball & Stick representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Draw bonds in tube
– Choose an object type for drawing bonds in tube representation
– Open the Atom Selection dialog box
– Click to select atoms for representation
– Double-click to apply to all atoms

Color all atoms by scheme
Choose a predefined color scheme.

Color residue by constant color
– Choose a color for applying to residues
– Click to select residues to color
– Double-click to color all atoms

Label atoms
– Choose a predefined label type
– Delete labels

Label picked atoms
– Choose an object type for labeling atoms
– Open the Atom Selection dialog box
– Open the Atom Labels panel at the Composition folder
– Delete labels
– Click to select atoms to label
– Double-click to label all atoms

Display H-bonds
– Choose bond type:
intra—displays H-bonds within the selected molecule
inter—displays H-bonds between the selected molecule and all other atoms.
– Delete H-bonds
– Click to select molecule

Measure distances, angles or dihedrals
– Choose a parameter for displaying measurements
– Delete measurements
– Click to select atoms for measurement

2.3.3 Mouse Functions in the Workspace

The left mouse button is used for selecting objects. You can either click on a single atom or bond, or you can drag to select multiple objects. The right mouse button opens shortcut menus, which are described in Section 2.7 of the *Maestro User Manual*.

The middle and right mouse buttons can be used on their own and in combination with the SHIFT and CTRL keys to perform common operations, such as rotating, translating, centering, adjusting, and zooming.

Table 2.1. Mapping of Workspace operations to mouse actions.

Mouse Button	Keyboard	Motion	Action
Left		click, drag	Select
Left	SHIFT	click, drag	Toggle the selection
Middle		drag	Rotate about X and Y axes Adjust bond, angle, or dihedral
Middle	SHIFT	drag vertically	Rotate about X axis
Middle	SHIFT	drag horizontally	Rotate about Y axis
Middle	CTRL	drag horizontally	Rotate about Z axis
Middle	SHIFT + CTRL	drag horizontally	Zoom
Right		click	Spot-center on selection
Right		click and hold	Display shortcut menu
Right		drag	Translate in the X-Y plane
Right	SHIFT	drag vertically	Translate along the X axis
Right	SHIFT	drag horizontally	Translate along the Y axis
Right	CTRL	drag horizontally	Translate along the Z axis
Middle & Right		drag horizontally	Zoom

2.3.4 Shortcut Key Combinations

Some frequently used operations have been assigned shortcut key combinations. The shortcuts available in the main window are described in Table 2.2.

Table 2.2. Shortcut keys in the Maestro main window.

Keys	Action	Equivalent Menu Choices
CTRL+B	Open Build panel	Edit > Build
CTRL+C	Create entry	Project > Create Entry From Workspace
CTRL+E	Open Command Script Editor panel	Edit > Command Script Editor
CTRL+F	Open Find Atoms panel	Edit > Find
CTRL+H	Open Help panel	Help > Help
CTRL+I	Open Import panel	Project > Import Structures
CTRL+M	Open Measurements panel	Tools > Measurements
CTRL+N	Create new project	Project > New
CTRL+O	Open project	Project > Open
CTRL+P	Print	Maestro > Print
CTRL+Q	Quit	Maestro > Quit
CTRL+S	Open Sets panel	Tools > Sets
CTRL+T	Open Project Table panel	Project > Show Table
CTRL+W	Close project	Project > Close
CTRL+Z	Undo/Redo last command	Edit > Undo/Redo
CTRL+=	Enter and exit full screen mode (Workspace occupies full screen)	None

2.4 Maestro Projects

All the work you do in Maestro is done within a *project*. A project consists of a set of *entries*, each of which contains one or more chemical structures and their associated data. In any Maestro session, there can be only one Maestro project open. If you do not specify a project when you start Maestro, a *scratch* project is created. You can work in a scratch project without saving it, but you must save it in order to use it in future sessions. When you save or close a project, all the view transformations (rotation, translation, and zoom) are saved with it. When you close a project, a new scratch project is automatically created.

Likewise, if there is no entry displayed in the Workspace, Maestro creates a *scratch* entry. Structures that you build in the Workspace constitute a scratch entry until you save the structures as project entries. The scratch entry is not saved with the project unless you explicitly add it to the project. However, you can use a scratch entry as input for some calculations.

To add a scratch entry to a project, do one of the following:

- Click the Create entry from Workspace button:

- Choose Create Entry from Workspace from the Project menu.
- Press CTRL+C.

In the dialog box, enter a name and a title for the entry. The entry name is used internally to identify the entry and can be modified by Maestro. The title can be set or changed by the user, but is not otherwise modified by Maestro.

Once an entry has been incorporated into the project, its structures and their data are represented by a row in the Project Table. Each row contains the row number, an icon indicating whether the entry is displayed in the Workspace (the In column), the entry title, a button to open the Surfaces panel if the entry has surfaces, the entry name, and any entry properties. The row number is not a property of the entry.

Entries can be collected into groups, and the members of the group can be displayed or hidden. Most additions of multiple entries to the Project Table are done as entry groups.

You can use entries as input for all of the computational programs—Glide, Impact, Jaguar, Liaison, LigPrep, MacroModel, Phase, Prime, QikProp, QSite, and Strike. You can select entries as input for the ePlayer, which displays the selected structures in sequence. You can also duplicate, combine, rename, and sort entries; create properties; import structures as entries; and export structures and properties from entries in various formats.

To open the Project Table panel, do one of the following:

- Click the Open/Close Project Table button on the toolbar

- Choose Show Table from the Project menu
- Press CTRL+T.

The Project Table panel contains a menu bar, a toolbar, and the table itself.

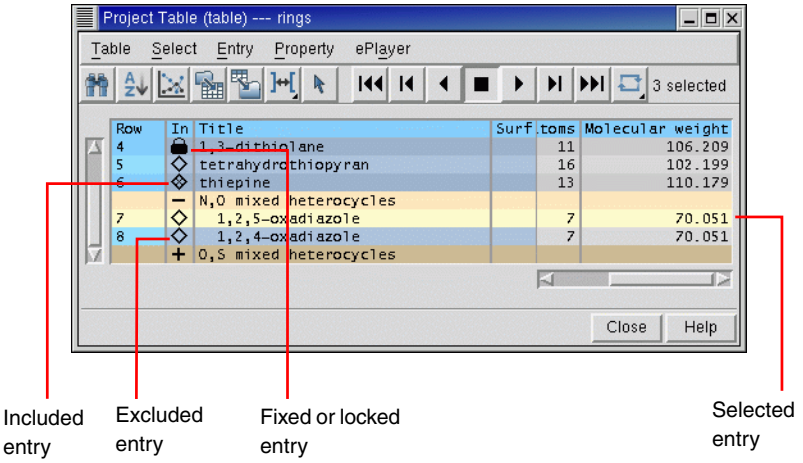

Figure 2.3. The** Project Table **panel.

2.4.1 The Project Table Toolbar

The Project Table toolbar contains two groups of buttons and a status display. The first set of buttons opens various panels that allow you to perform functions on the entries in the Project Table. The second set of buttons controls the ePlayer, which "plays through" the selected structures: each structure is displayed in the Workspace in sequence, at a given time interval. See Section 2.3.2 on page 7 for a description of the types of toolbar buttons. The buttons are described below.

Find
Open the Find panel for locating alphanumeric text in any column of the Project Table, except for the row number.

Sort
Open the Sort panel for sorting entries by up to three properties.

Plot
Open the Plot panel for plotting entry properties.

Import Structure
Open the Import panel for importing structures into the project.

Export Structure
Open the Export panel for exporting structures to a file.

Columns
Choose an option for adjusting the column widths.

Select only
Open the Entry Selection dialog box for selecting entries based on criteria for entry properties.

Go to start
Display the first selected structure.

Previous
Display the previous structure in the list of selected structures.

Play backward
Display the selected structures in sequence, moving toward the first.

Stop
Stop the ePlayer.

Play forward
Display the selected structures in sequence, moving toward the last.

Next
Display the next structure in the list of selected structures.

Go to end
Display the last selected structure.

Loop
Choose an option for repeating the display of the structures. Single Direction displays structures in a single direction, then repeats. Oscillate reverses direction each time the beginning or end of the list is reached.

The status display, to the right of the toolbar buttons, shows the number of selected entries. When you pause the cursor over the status display, the Balloon Help shows the total number of entries, the number shown in the table, the number selected, and the number included in the Workspace.

2.4.2 The Project Table Menus

- Table—find text, sort entries, plot properties, import and export structures, and configure the Project Table.
- Select—select all entries, none, invert your selection, or select classes of entries using the Entry Selection dialog box and the Filter panel.
- Entry—include or exclude entries from the Workspace, display or hide entries in the Project Table, and perform various operations on the selected entries.

- Property—display and manipulate entry properties in the Project Table.
- ePlayer—view entries in succession, stop, reverse, and set the ePlayer options.

2.4.3 Selecting Entries

Many operations in Maestro are performed on the entries selected in the Project Table. The Project Table functions much like any other table: select rows by clicking, shift-clicking, and control-clicking. However, because clicking in an editable cell of a selected row enters edit mode, you should click in the Row column to select entries. See Section 2.4.5 on page 16 for more information on mouse actions in the Project Table. There are shortcuts for selecting classes of entries on the Select menu.

In addition to selecting entries manually, you can select entries that meet a combination of conditions on their properties. Such combinations of conditions are called *filters*. Filters are Entry Selection Language (ESL) expressions and are evaluated at the time they are applied. For example, if you want to set up a Glide job that uses ligands with a low molecular weight (say, less than 300) and that has certain QikProp properties, you can set up a filter and use it to select entries for the job. If you save the filter, you can use it again on a different set of ligands that meet the same selection criteria.

To create a filter:

1. Do one of the following:
   - Choose Only, Add, or Deselect from the Select menu.
   - Click the Entry selection button on the toolbar.

   
2. In the Properties folder, select a property from the property list, then select a condition.
3. Combine this selection with the current filter by clicking Add, Subtract, or Intersect. These buttons perform the Boolean operations OR, AND NOT, and AND on the corresponding ESL expressions.
4. To save the filter for future use click Create Filter, enter a name, and click OK.
5. Click OK to apply the filter immediately.

2.4.4 Including Entries in the Workspace

In addition to selecting entries, you can also use the Project Table to control which entries are displayed in the Workspace. An entry that is displayed in the Workspace is *included* in the Workspace; likewise, an entry that is not displayed is *excluded*. Included entries are marked by an X in the diamond in the In column; excluded entries are marked by an empty diamond. Entry inclusion is completely independent of entry selection.

To include or exclude entries, click, shift-click, or control-click in the In column of the entries, or select entries and choose Include or Exclude from the Entry menu. Inclusion with the mouse works just like selection: when you include an entry by clicking, all other entries are excluded.

It is sometimes useful to keep one entry in the Workspace and include others one by one: for example, a receptor and a set of ligands. You can fix the receptor in the Workspace by selecting it in the Project Table and choosing Fix from the Entry menu or by pressing CTRL+F. A padlock icon replaces the diamond in the In column to denote a *fixed* entry. To remove a fixed entry from the Workspace, you must exclude it explicitly (CTRL+X). It is not affected by the inclusion or exclusion of other entries. Fixing an entry affects only its inclusion; you can still rotate, translate, or modify the structure.

2.4.5 Mouse Functions in the Project Table

The Project Table supports the standard use of shift-click and control-click to select objects. This behavior applies to the selection of entries and the inclusion of entries in the Workspace. You can also drag to resize rows and columns and to move rows.

You can drag a set of non-contiguous entries to reposition them in the Project Table. When you release the mouse button, the entries are placed after the first unselected entry that precedes the entry on which the cursor is resting. For example, if you select entries 2, 4, and 6, and release the mouse button on entry 3, these three entries are placed after entry 1, because entry 1 is the first unselected entry that precedes entry 3. To move entries to the top of the table, drag them above the top of the table; to move entries to the end of the table, drag them below the end of the table.

A summary of mouse functions in the Project Table is provided in Table 2.3.

Table 2.3. Mouse operations in the Project Table.

Task	Mouse Operation
Change a Boolean property value	Click repeatedly in a cell to cycle through the possible values (On, Off, Clear)
Display the Entry menu for an entry	Right-click anywhere in the entry. If the entry is not selected, it becomes the selected entry. If the entry is selected, the action is applied to all selected entries.
Display a version of the Property menu for a property	Right-click in the column header
Edit the text or the value in a table cell	Click in the cell and edit the text or value
Include an entry in the Workspace, exclude all others	Click the In column of the entry
Move selected entries	Drag the entries
Paste text into a table cell	Middle-click
Resize rows or columns	Drag the boundary with the middle mouse button
Select an entry, deselect all others	For an unselected entry, click anywhere in the row except the In column; for a selected entry, click the row number.
Select or include multiple entries	Click the first entry then shift-click the last entry
Toggle the selection or inclusion state	Control-click the entry or the In column

2.4.6 Project Table Shortcut Keys

Some frequently used project operations have been assigned shortcut key combinations. The shortcuts, their functions, and their menu equivalents are listed in Table 2.4.

Table 2.4. Shortcut keys in the Project Table.

Keys	Action	Equivalent Menu Choices
CTRL+A	Select all entries	Select > All
CTRL+F	Fix entry in Workspace	Entry > Fix
CTRL+I	Open Import panel	Table > Import Structures
CTRL+N	Include only selected entries	Entry > Include Only
CTRL+U	Deselect all entries	Select > None
CTRL+X	Exclude selected entries	Entry > Exclude
CTRL+Z	Undo/Redo last command	Edit > Undo/Redo in main window

2.5 Building a Structure

After you start Maestro, the first task is usually to create or import a structure. You can open existing Maestro projects or import structures from other sources to obtain a structure, or you can build your own. To open the Build panel, do one of the following:

- Click the Open/Close Build panel button in the toolbar:

- Choose Build from the Edit menu.
- Press CTRL+B.

The Build panel allows you to create structures by drawing or placing atoms or fragments in the Workspace and connecting them into a larger structure, to adjust atom positions and bond orders, and to change atom properties. This panel contains a toolbar and three folders.

2.5.1 Placing and Connecting Fragments

The Build panel provides several tools for creating structures in the Workspace. You can place and connect fragments, or you can draw a structure freehand.

To place a fragment in the Workspace:

1. Select Place.
2. Choose a fragment library from the Fragments menu.
3. Click a fragment.
4. Click in the Workspace where you want the fragment to be placed.

To connect fragments in the Workspace, do one of the following:

- Place another fragment and connect them using the Connect & Fuse panel, which you open from the Edit menu on the main menu bar or with the Display Connect & Fuse panel on the Build toolbar.

- Replace one or more atoms in the existing fragment with another fragment by selecting a fragment and clicking in the Workspace on the main atom to be replaced.
- Grow another fragment by selecting Grow in the Build panel and clicking the fragment you want to add in the Fragments folder.

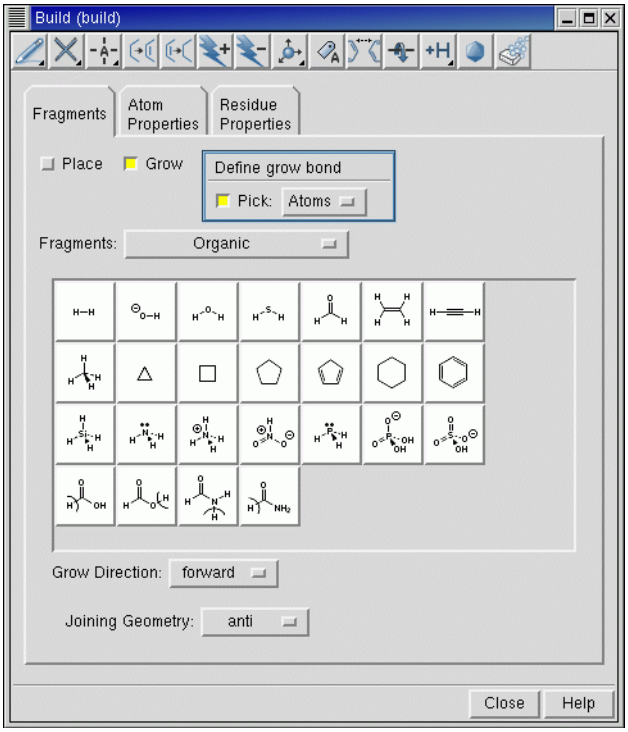

Figure 2.4. The* Build *panel.

Grow mode uses predefined rules to connect a fragment to the *grow bond*. The grow bond is marked by a green arrow. The new fragment replaces the atom at the head of the arrow on the grow bond and all atoms attached to it. To change the grow bond, choose Bonds from the Pick option menu in the Build panel and click on the desired grow bond in the Workspace. The arrow points to the atom nearest to where you clicked.

To draw a structure freehand:

1. Choose an element from the Draw button menu on the Build panel toolbar:

   

2. Click in the Workspace to place an atom of that element.
3. Click again to place another atom and connect it to the previous atom.
4. Continue this process until you have drawn the structure.
5. Click the active atom again to finish drawing.

2.5.2 Adjusting Properties

In the Atom Properties folder, you can change the properties of the atoms in the Workspace. For each item on the Property option menu—Element, Atom Type (MacroModel), Partial Charge, PDB Atom Name, Grow Name, and Atom Name—there is a set of tools you can use to change the atom properties. For example, the Element tools consist of a periodic table from which you can choose an element and select an atom to change it to an atom of the selected element.

Similarly, the Residue Properties folder provides tools for changing the properties of residues: the Residue Number, the Residue Name, and the Chain Name.

To adjust bond lengths, bond angles, dihedral angles, and chiralities during or after building a structure, use the Adjust distances, angles or dihedrals button on the main toolbar:

You can also open the Adjust panel from this button menu, from the Display Adjust panel button on the Build panel toolbar (which has the same appearance as the above button) or from the Edit menu in the main window.

2.5.3 The Build Panel Toolbar

The toolbar of the Build panel provides quick access to tools for drawing and modifying structures and labeling atoms. See Section 2.3.2 on page 7 for a description of the types of toolbar buttons. The toolbar buttons and their use are described below.

Free-hand drawing
Choose an element for drawing structures freehand in the Workspace (default C). Each click in the Workspace places an atom and connects it to the previous atom.

Delete
Choose an object for deleting. Same as the Delete button on the main toolbar, see page 8.

Set element
Choose an element for changing atoms in the Workspace (default C). Click an atom to change it to the selected element.

Increment bond order
Select a bond to increase its bond order by one, to a maximum of 3.

Decrement bond order
Select a bond to decrease its bond order by one, to a minimum of 0.

Increment formal charge
Select an atom to increase its formal charge by one.

Decrement formal charge
Select an atom to decrease its formal charge by one.

Move
Choose a direction for moving atoms, then click the atom to be moved. Moves in the XY plane are made by clicking the new location. Moves in the Z direction are made in 0.5 Å increments.

Label
Apply heteroatom labels as you build a structure. The label consists of the element name and formal charge, and is applied to atoms other than C and H.

Display Connect & Fuse panel
Open the Connect & Fuse panel so you can connect structures (create bonds between structures) or fuse structures (replace atoms of one structure with those of another).

Display Adjust panel
Open the Adjust panel so you can change bond lengths, bond angles, dihedral angles, or atom chiralities.

Add hydrogens
Choose an atom type for applying the current hydrogen treatment. Same as the Add hydrogens button on the main toolbar, see page 8.

Geometry Symmetrizer
Open the Geometry Symmetrizer panel for symmetrizing the geometry of the structure in the Workspace.

Geometry Cleanup
Clean up the geometry of the structure in the Workspace.

2.6 Selecting Atoms

Maestro has a powerful set of tools for selecting atoms in a structure: toolbar buttons, picking tools in panels, and the Atom Selection dialog box. These tools allow you to select atoms in two ways:

- Select atoms first and apply an action to them
- Choose an action first and then select atoms for that action

2.6.1 Toolbar Buttons

The small triangle in the lower right corner of a toolbar button indicates that the button contains a menu. Many of these buttons allow you to choose an object type for selecting: choose Atoms, Bonds, Residues, Chains, Molecules, or Entries, then click on an atom in the Workspace to perform the action on all the atoms in that structural unit.

For example, to select atoms with the Workspace selection toolbar button:

1. Choose Residues from the Workspace selection button menu:

   

   The button changes to:

   

2. Click on an atom in a residue in the Workspace to select all the atoms in that residue.

2.6.2 Picking Tools

The picking tools are embedded in each panel in which you need to select atoms to apply an operation. The picking tools in a panel can include one or more of the following:

- Pick option menu—Allows you to choose an object type. Depending on the operation to be performed, you can choose Atoms, Bonds, Residues, Chains, Molecules, or Entries, then click on an atom in the Workspace to perform the action on all the atoms in that structural unit.

  The Pick option menu varies from panel to panel, because not all object types are appropriate for a given operation. For example, some panels have only Atoms and Bonds in the Pick option menu.

- All button—Performs the action on all atoms in the Workspace.
- Selection button—Performs the action on any atoms already selected in the Workspace.
- Previous button—Performs the action on the most recent atom selection defined in the Atom Selection dialog box.
- Select button—Opens the Atom Selection dialog box.
- ASL text box—Allows you to type in an ASL expression for selecting atoms.

  ASL stands for Atom Specification Language, and is described in detail in the *Maestro Command Reference Manual*.

- Clear button—Clears the current selection

  

- Show markers option—Marks the selected atoms in the Workspace.

For example, to label atoms with the Label Atoms panel:

1. Choose Atom Labels from the Display menu.
2. In the Composition folder, select Element and Atom Number.
3. In the picking tools section at the top of the panel, you could do one of the following:
   - Click Selection to apply labels to the atoms already selected in the Workspace (from the previous example).
   - Choose Residues from the Pick option menu and click on an atom in a different residue to label all the atoms in that residue.

2.6.3 The Atom Selection Dialog Box

If you wish to select atoms based on more complex criteria, you can use the Atom Selection dialog box. To open this dialog box, choose Select from a button menu or click the Select button in a panel. See Section 5.3 of the *Maestro User Manual* for detailed instructions on how to use the Atom Selection dialog box.

2.7 Scripting in Maestro

Although you can perform nearly all Maestro-supported operations through menus and panels, you can also perform operations using Maestro commands, or compilations of these commands, called *scripts*. Scripts can be used to automate lengthy procedures or repetitive tasks and can be created in several ways. These are summarized below.

2.7.1 Python Scripts

Python is a full-featured scripting language that has been embedded in Maestro to extend its scripting facilities. The Python capabilities within Maestro include access to Maestro functionality for dealing with chemical structures, projects, and Maestro files.

The two main Python commands used in Maestro are:

- `pythonrun`—executes a Python module. (You can also use the alias `pyrun`.) The syntax is:

  `pythonrun` *module*`.`*function*

- `pythonimport`—rereads a Python file so that the next time you use the `pythonrun` command, it uses the updated version of the module. (You can also use the alias `pyimp`.)

From the Maestro Scripts menu you can install, manage, and run Python scripts. For more information on the Scripts menu, see Section 13.1 of the *Maestro User Manual*.

For more information on using Python with Maestro, see *Scripting with Python*.

2.7.2 Command Scripts

All Maestro commands are logged and displayed in the Command Script Editor panel. This means you can create a command script by performing the operations with the GUI controls, copying the logged commands from the Command History list into the Script text area of the panel, then saving the list of copied commands as a script.

To run an existing command script:

1. Open the Command Script Editor panel from the Edit menu in the main window.
2. Click Open Local and navigate to the directory containing the desired script.
3. Select a script in the Files list and click Open.

   The script is loaded into the Script window of the Command Script Editor panel.
4. Click Run Script.

Command scripts cannot be used for Prime operations.

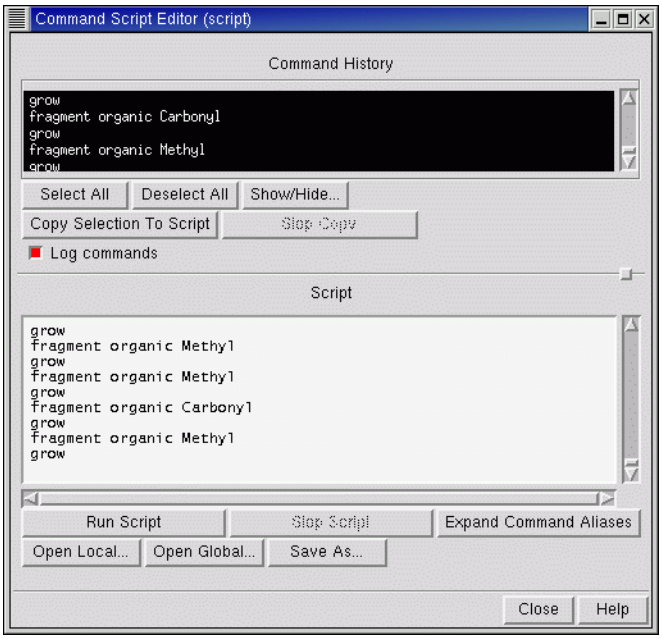

Figure 2.5. The Command Script Editor ***panel.***

2.7.3 Macros

There are two kinds of macros you can create: named macros and macros assigned to function keys F1 through F12.

To create and run a named macro:

1. Open the Macros panel from the Edit menu in the main window.
2. Click New, enter a name for the macro, and click OK.
3. In the Definition text box, type the commands for the macro.
4. Click Update to update the macro definition.
5. To run the macro, enter the following in the command input area in the main window:

   `macrorun` *macro-name*

   If the command input area is not visible, choose Command Input Area from the Display menu.

To create and run a function key macro:

1. Open the Function Key Macros panel from the Edit menu in the main window.
2. From the Macro Key option, select a function key (F1 through F12) to which to assign the macro.
3. In the text box, type the commands for the macro.
4. Click Run to test the macro or click Save to save it.
5. To run the macro from the main window, press the assigned function key.

For more information on macros, see Section 13.5 of the *Maestro User Manual*.

2.8 Specifying a Maestro Working Directory

When you use Maestro to launch SiteMap jobs, Maestro writes job output to the directory specified in the Directory folder of the Preferences panel. By default, this directory (the file I/O directory) is the directory from which you started Maestro.

To change the Maestro working directory:

1. Open the Preferences panel from the Maestro menu.
2. Click the Directory tab.
3. Select the directory you want to use for reading and writing files.

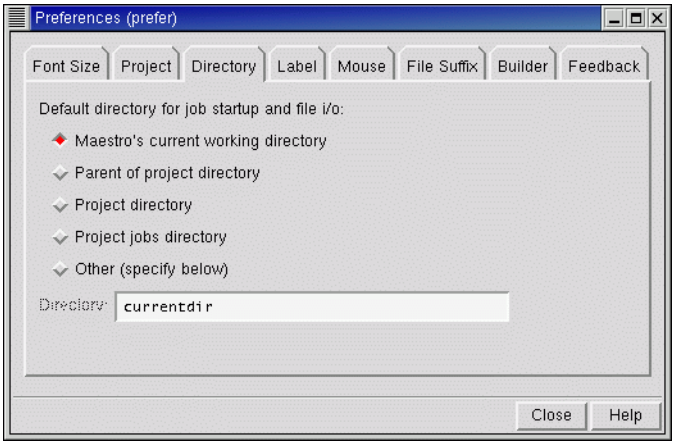

Figure 2.6. The** Directory **folder of the** Preferences **panel.

You can also set other preferences in the Preferences panel. See Section 12.2 of the *Maestro User Manual* for details.

2.9 Undoing an Operation

To undo a single operation, click the Undo button in the toolbar, choose Undo from the Edit menu, or press CTRL+Z. The word Undo in the menu is followed by text that describes the operation to undo. Not all operations can be undone: for example, global rotations and translations are not undoable operations. For such operations you can use the Save view and Restore view buttons in the toolbar, which save and restore a molecular orientation.

2.10 Running and Monitoring Jobs

Maestro has panels for each product for preparing and submitting jobs. To use these panels, choose the appropriate product and task from the Applications menu and its submenus. Set the appropriate options in the panel, then click Start to open the Start dialog box and set options for running the job. For a complete description of the Start dialog box associated with your computational program, see your product's User Manual. When you have finished setting the options, click Start to launch the job and open the Monitor panel.

The Monitor panel is the control panel for monitoring the progress of jobs and for pausing, resuming, or killing jobs. All jobs that belong to you can be displayed in the Monitor panel, whether or not they were started from Maestro. Subjobs are indented under their parent in the job list. The text pane shows output information from the monitored job, such as the contents

of the log file. The Monitor panel opens automatically when you start a job. If it is not open, you can open it by choosing Monitor from the Applications menu in the Maestro main window.

While jobs are running, the Detach, Pause, Resume, Stop, Kill, and Update buttons are active. When there are no jobs currently running, only the Monitor and Delete buttons are active. These buttons act on the selected job. By default, only jobs started from the current project are shown. To show other jobs, deselect Show jobs from current project only.

When a monitored job ends, the results are incorporated into the project according to the settings used to launch the job. If a job that is not currently being monitored ends, you can select it in the Monitor panel and click Monitor to incorporate the results. Monitored jobs are incorporated only if they are part of the current project. You can monitor jobs that are not part of the current project, but their results are not incorporated. To add their results to a project, you must open the project and import the results.

Further information on job control, including configuring your site, monitoring jobs, running jobs, and job incorporation, can be found in the *Job Control Guide* and the *Installation Guide*.

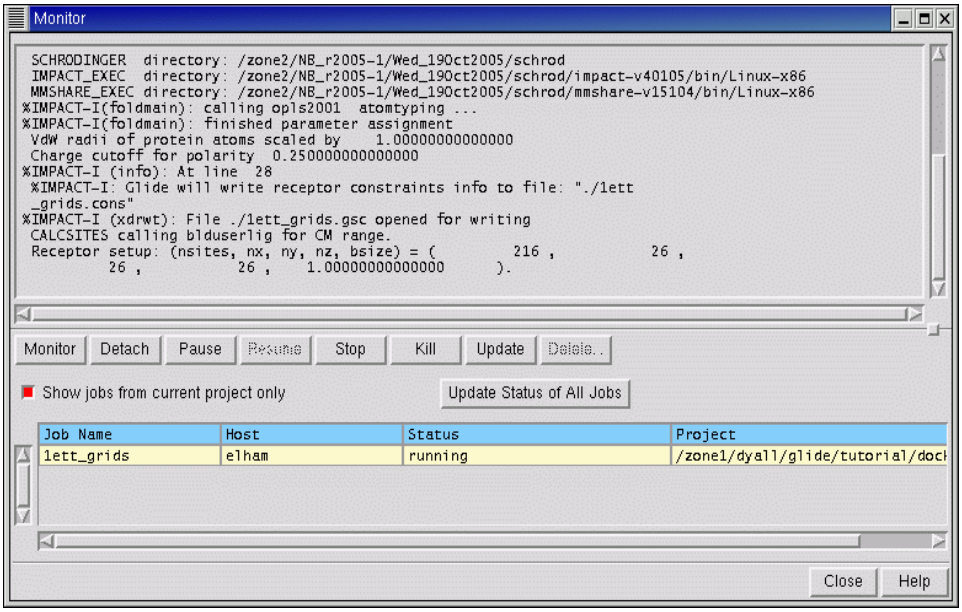

Figure 2.7. The* Monitor *panel.

2.11 Getting Help

Maestro comes with automatic, context-sensitive help (Auto-Help), Balloon Help (tooltips), an online help facility, and a user manual. To get help, follow the steps below:

- Check the Auto-Help text box at the bottom of the main window. If help is available for the task you are performing, it is automatically displayed there. It describes what actions are needed to perform the task.
- If your question concerns a GUI element, such as a button or option, there may be Balloon Help for the item. Pause the cursor over the element. If the Balloon Help does not appear, check that Show Balloon Help is selected in the Help menu of the main window. If there is Balloon Help for the element, it appears within a few seconds.
- If you do not find the help you need using either of the steps above, click the Help button in the lower right corner of the appropriate panel. The Help panel is displayed with a relevant help topic.
- For help with a concept or action not associated with a panel, open the Help panel from the Help menu or press CTRL+H.

If you do not find the information you need in the Maestro help system, check the following sources:

- The *Maestro User Manual*
- The Frequently Asked Questions page on the Schrödinger Support Center.

You can also contact Schrödinger by e-mail or phone for help:

- E-mail: help@schrodinger.com
- Phone: (503) 299-1150

2.12 Ending a Maestro Session

To end a Maestro session, choose Quit from the Maestro menu. To save a log file with a record of all operations performed in the current session, click Quit, save log file in the Quit panel. This information can be useful to Schrödinger support staff when responding to any problem you report.

How SiteMap Works

SiteMap 2.0 represents an expansion of the original SiteMap facility in Maestro. As in the original procedure [3], site mapping operates in a manner analogous to Goodford's GRID algorithm [4]. A SiteMap calculation has three stages. First, a grid is set up, and the points are grouped into sets according to various criteria to to define the sites. Second, the sites are mapped on another grid to produce files for visualization of the maps. Finally, properties are evaluated and sites are written in a Maestro-readable form. Each stage is accomplished by running an Impact job. The three stages are described in the sections below.

3.1 Finding Sites

The first stage of a SiteMap calculation is to locate the sites. A *site* is defined by a set of site points on a grid that are either contiguous or bridged by short gaps in solvent-exposed regions. The site-finding algorithm begins by placing a 1-Å grid of possible site points around the entire protein or around a placeholder species, such as a ligand. Identifying the sites involves several steps.

The first step is to classify the grid points as being either "inside" or "outside" the protein. The distance from each grid point to nearby protein atoms is compared to the van der Waals radius of each protein atom. If the ratio of the squares of these distances is larger than a given threshold, the point is considered to be outside the protein.

In the next step, the "outside" points are examined to determine which ones are in sufficiently good van der Waals contact with the receptor and sufficiently enclosed by the receptor to serve as site points. Enclosure is defined by sampling all possible directions from the grid point and determining the fraction of these directions ("rays") that strike the surface within a given distance. If the fraction is larger than a given threshold, the point is sufficiently enclosed and is therefore a candidate site point. The contact with the receptor is determined by a cutoff on the van der Waals interaction energy at the site point: if the interaction energy is too small in magnitude, the point is rejected. Points that meet all criteria are added to the list of site points.

The third step combines site points into distinct site-point groups. For a site point to be considered for membership in a group, it must have a minimum number of candidate site points within a given distance. Site points that do not have this minimum number are discarded. The process starts by assigning a site point to a group, then adding all candidate site points within a prescribed minimum distance. The addition process is repeated for each new site point. When

no further site points can be added, the group is considered complete and another site-point group is initiated. The process continues until all site points have been examined.

The final step merges site-point groups when the gap between them is relatively small and occurs in a solvent-exposed region. The merge is controlled by user-adjustable thresholds that determine how close two site-point groups must be for them to be considered for merging and whether the gap between them could plausibly be bridged by ligand atoms. The final groups constitute the sites.

The sites are written in order of the number of site points they contain to a Maestro file. Each site point is represented by a dummy atom, and zero-order bonds are used to join the site points for each site into a "structure" that Maestro recognizes as a single molecule.

3.2 Mapping the Sites

The second stage of a SiteMap calculation generates the various "maps" that define the sites. A map is defined by a set of values of a property on a given 3D grid. First, SiteMap uses the site points from the preceding stage to position a mapping box for each site. This box defines a grid with a given spacing, and extends beyond the site by a given amount.

Van der Waals and distance-dependent electrostatic-interactions of a probe placed at each of the grid points are then used to generate van der Waals and electric-field grids. The probe simulates a water molecule, and is represented by a van der Waals sphere of radius 1.6 Å, a well depth of 0.13 kcal/mol, and a point dipole moment of 2.4 Debye. To form the electrostatic-field grid, the probe's point dipole is oriented along the electric field and is offset by 0.15 Å from the van der Waals sphere toward the center of an optimally oriented O–H bond.

To more accurately represent the expected contact positions and interaction energies of donor and acceptor atoms, the force field is first modified by adjusting van der Waals radii and by reducing formal-charge contributions to the partial atomic charges by 50%. The reduction in formal charges, like the one employed in Glide [6], is used to keep regions around formally charged groups from inappropriately dominating the maps, which are meant to reflect interactions in solvent, not in the gas phase.

The resultant van der Waals and electric-field grids are then used to generate the phobic and philic potentials. Using these potentials, SiteMap partitions the accessible space in each site into the following three basic types of regions:

- Hydrophobic—regions that are favorable for occupancy by hydrophobic ligand groups
- Hydrophilic—regions that are favorable for occupancy by hydrophilic ligand groups
- Neither hydrophobic nor hydrophilic—regions that are of mixed character or are far enough from the receptor surface to be similar to bulk water

The hydrophilic regions are further subdivided into hydrogen-bond donor, hydrogen-bond acceptor, and metal-binding regions. The hydrophobic and hydrophilic regions (or maps) are obtained by contouring the computed phobic and philic potentials at specified threshold values. The "neither" regions are implicit: these are regions that lie outside the protein but are not marked as being either hydrophobic or hydrophilic. The methods for obtaining the maps are described in more detail in the sections below.

For each site, the five maps—hydrophilic, hydrophobic, donor, acceptor, and surface—are written to files (`.grd` files and `.vis` files) that can be used by Maestro to display the surfaces. If there is a metal, the metal-binding map is also written out.

3.2.1 Hydrophilic Map

SiteMap constructs a measure of hydrophilicity by adding an "electric-field reward" term to the van der Waals energy:

Grid_philic = vdW_energy + oriented-dipole_energy

where the oriented-dipole energy is necessarily negative. Hydrophilic regions are those within which the sum of the two terms is more negative than a given threshold, which by default is –8 kcal/mol.

3.2.2 Hydrophobic Map

The quantity representing hydrophobicity is constructed by adding an "electric-field penalty" (positive) term to the van der Waals term:

Grid_phobic = vdW_energy – 0.30 * oriented-dipole_energy

Hydrophobic regions thus are regions where something would like to be, but water would not. The starting point for defining the hydrophobic regions is to consider the regions within which the sum of the two terms is more negative than a given threshold.

SiteMap offers several alternatives for the definition of hydrophobic regions. The least restrictive definition uses a threshold of –0.75 kcal/mol, and includes all site points that lie within this region. This is not the default behavior, but represents the original SiteMap definition. The more restrictive definitions involve two possible modifications to the hydrophobic region.

In the first, grid points that border on too many assigned philic points, that have too few phobic-point or "inside-protein" neighbors, or that border on too many free-space "outside" points are reclassified as non-phobic.

In the second, for each phobic grid point the fraction of radial rays that intersect the protein surface within a given distance (default 6 Å) is calculated, and the phobic potential is then

multiplied by this fraction. By scaling down the phobic potential, exposed regions are less favored than regions that are sheltered from the solvent, like the Glide XP detection of "phobic enclosure" [6]. The threshold for defining the phobic region is also reduced, to –0.50 kcal/mol. This modification considers the nature of the site beyond the immediate vicinity of the grid point, in a way that the first modification cannot.

The default behavior is to include both of these modifications.

3.2.3 Donor, Acceptor, and Metal-Binding Regions

The hydrophilic map is further partitioned into separate hydrogen-bond donor and acceptor maps. When there is interaction with a metal center other than Ca^{2+}, which (as in Glide XP) is not considered to be a metal-binding center, a separate metal-binding map is also formed. Metal-binding grid points are philic grid points that lie within 3 Å of a qualifying metal center. Classification of the remaining philic points as donor or acceptor points is made by displacing them in the direction of the local electrostatic field and recomputing the value of the field. Donor and acceptor points are assigned depending on whether this displacement increases or decreases the magnitude of the field.

3.2.4 Surface Map

The surface map is obtained by removing attractive regions of the van der Waals grid and then contouring the repulsive part of this grid at a positive threshold value, which is set to +1 kcal/mol by default.

3.3 Evaluating the Sites

This stage uses the site-point groups produced in the site-finding stage and the grids produced in the mapping stage to evaluate the sites in terms of a number of properties. The same modifications to van der Waals radii and formal-charge contributions and the same definition of hydrophobicity are used as in the mapping stage. The properties for each site are added to the Maestro file for the site and recorded in the log file.

To minimize grid errors, the contact, phil, and don/acc SiteMap properties are calculated explicitly as average values computed at the site-point positions (including extension points), but the more complicated phob property is obtained by interpolation from the phobic grid file produced in the site-visualization step.

To make it easy to recognize sites that appear to be unusually favorable or deficient, key properties are expressed relative to the average value found for a large number of tight-binding (≤ 1 μM) sites. The procedure by which this average was obtained is described in Chapter 5. The properties and their use are described below.

SiteScore. The SiteScore is based on a weighted sum of several of the properties that are discussed below. This score is constructed and calibrated so that the average SiteScore for 157 investigated submicromolar sites is 1.0. Thus, a score of greater than 1 suggests a site of particular promise. A SiteScore of 0.80 has been found to accurately distinguish between drug-binding and non-drug-binding sites (see Chapter 5).

Number of Site Points. The number of site points that make up the site is a measure of the size of the site. As a rough rule of thumb, 2 to 3 site points typically correspond to each atom of the bound ligand, including hydrogens. The size of the site is often a good indicator of the preferred binding site.

Exposure and Enclosure. These two properties provide different measures of how open the site is to solvent.

To evaluate the exposure property, "extension" site points are added on the 1-Å grid. These points must lie within a given distance in *x*, *y*, or *z* from an original site point (by default 3 Å), and must make good contact with the receptor or lie at least 4 Å from the nearest protein atom. The value of the property is the ratio of the number of extension points to the number of original plus extension points. A shallow, open site would allow many more site points to be added, giving a high exposure score. The lower the score, the better; the average for the tight-binding sites investigated is 0.49.

To evaluate the enclosure property, radial rays are drawn from the site points to sample all possible directions. The enclosure score is the fraction of rays that strike the receptor surface within a distance of 10 Å, averaged over the original and the extension site points used in the exposure evaluation. The receptor surface is the same surface that was used to classify grid points as outside or inside the protein in the site-finding step. Here, higher scores are better, with the average enclosure score for a tight-binding site being 0.78.

Contact. The contact property measures how strongly the average site point interacts with the surrounding receptor via van der Waals nonbonded interactions, when the site point is given nominal van der Waals parameters. The contact score has been calibrated so that the average score for a tight-binding site is 1.0.

Hydrophobic and hydrophilic character, and Balance. These properties, labeled "phob" and "phil", measure the relative hydrophobic and hydrophilic character of the site. The "balance" property expresses the ratio of the two. The phobic and philic scores have been calibrated so that the average score for a tight-binding site is 1.0. The average balance score for the investigated tight-binding sites, on the other hand is 1.6, not 1.0, because sites that have high phobic and low philic scores make large contributions to the average.

Donor/Acceptor character. This property, labeled "don/acc", indicates the degree to which a well-structured ligand might be expected to donate, rather than accept, hydrogen bonds, as inferred from the sizes and intensities of donor and acceptor SiteMap regions.

Reference distance properties. When a supplied ligand or other species is used to define the region of the receptor to be mapped, "refdist" and "refmin" properties are also computed. The first of these specifies the distance between the centroid of the site points and the centroid of the reference ligand. The second specifies the closest approach of a site point to a ligand atom. Both are given in angstroms.

In some cases, a small refmin value (typically < 1 Å) is accompanied by a moderately large refdist of 5 – 10 Å. These are cases in which the site extends asymmetrically beyond the reference ligand in one or more directions. In an endoprotease, such extensions may well map the channels that bind the N-terminal and C-terminal strands of the peptide undergoing cleavage, and hence are to be expected. These extensions are of interest because they may represent regions that a tight-binding ligand might usefully probe.

Running SiteMap

SiteMap can be run from within an existing Maestro session or from the command line. The original SiteMap facility is now accessible from the Surfaces submenu of the Display menu as Hydrophobic/philic.

4.1 Running SiteMap from Maestro

SiteMap calculations can be set up and run from the SiteMap panel, which is shown in Figure 4.1. To open this panel, choose SiteMap from the Applications menu. The panel is divided into three sections, Job options, Specify task, and Settings, which are described below. When you have finished making settings, click Start to start the job.

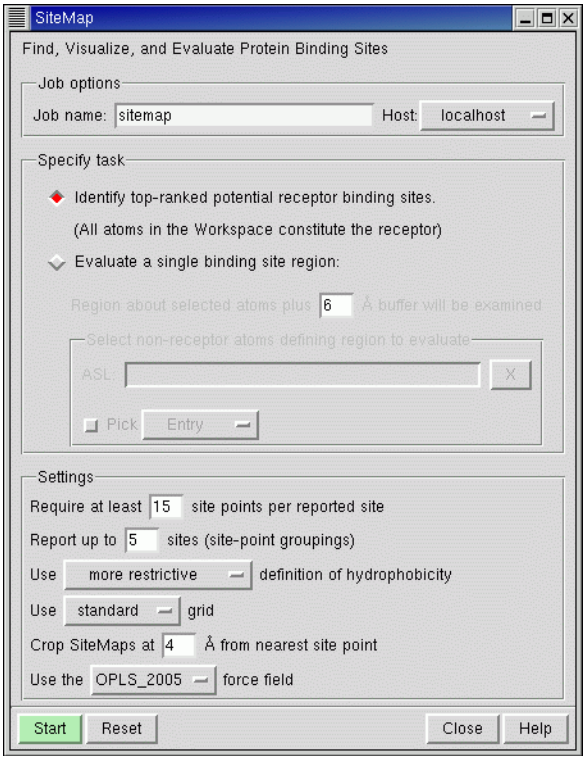

Figure 4.1. SiteMap panel showing options for mapping an entire protein.

4.1.1 Setting Job Options

In the Job options section, you can enter a name in the Job name text box, and select a host on which to run the job from the Host option menu. Since it only takes a few minutes to run a job for a protein having up to 5000 atoms, there is little reason to run the job on a remote host. The job name is used to name the output files.

4.1.2 Specifying the Task

In the Specify task section, you can choose between two tasks:

- Identify top-ranked potential receptor binding sites
- Evaluate a single binding site region

For each task, the structure to be used must be displayed in the Workspace.

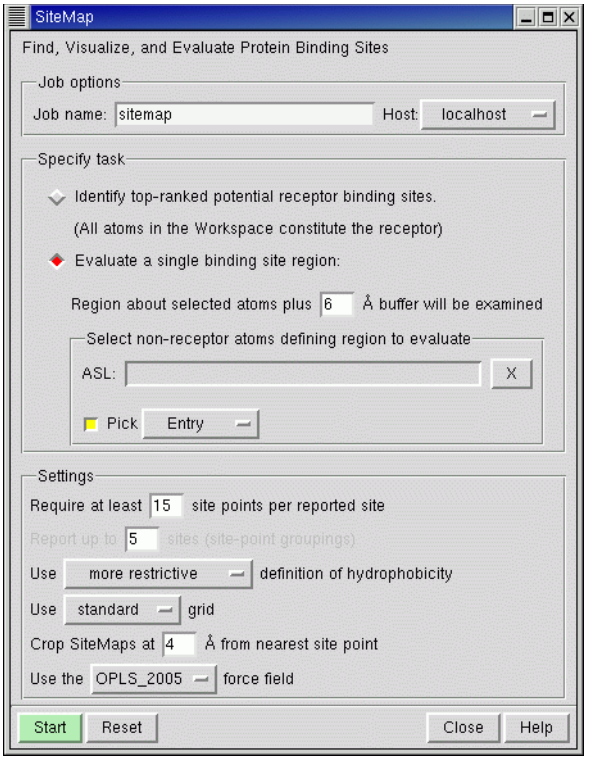

Figure 4.2. SiteMap panel showing options for mapping a region defined by a set of atoms.

If you choose the first task, Identify top-ranked potential receptor binding sites, SiteMap looks for binding sites on the entire protein structure. The protein structure must be displayed in the Workspace, and should consist only of the protein—no ligand, waters, or cofactors. Figure 4.1 shows the SiteMap panel when this task is chosen.

If you choose the second task, Evaluate a single binding site region, SiteMap restricts the search for binding sites on the protein to a region around a specified structure. When you select this option, the controls below it become available. Figure 4.2 shows the SiteMap panel when this task is chosen.

For this task, you must pick a single molecule or entry in the Workspace to define the binding site, by choosing Molecule or Entry from the Pick menu in the Select non-receptor atoms defining region to evaluate section., and picking an atom in the Workspace. The ASL text box above the Pick menu displays the ASL expression for the selected structure. You can clear the selection by clicking the X button, to the right of the ASL text box. The structure that you pick must not be the protein, and the contents of the Workspace must include only the protein and the structure you select to define the binding site.

If you want to include more than one molecule in the region for mapping (for example, a ligand and a cofactor), you should create an entry that includes only the molecules you want to use, and another entry for the receptor. You can then display both entries, and pick the entry that contains the two molecules to define the region.

The region to be added around the selected reference molecule or entry extends out from the reference by 6 Å, by default. If you want to change the extent of the region, you can enter a value in the Region about selected atoms plus *n* Å buffer will be examined text box.

4.1.3 Setting Other Options

In the Settings section, you can make the following choices to control the calculations:

- Require at least *n* site points per reported site—Enter a value to set the minimum number of site points required in the initial site-finding stage to define a site. The default value of 15 site points should allow even relatively small sites to be detected. The average number of site points found for the tight-binding sites investigated in the calibration studies (see Chapter 5) is about 150.

  SiteMap always reports at least one site as long as that site contains at least 3 site points, which is the minimum number required to recognize a site. Thus, only the second and subsequent sites, ranked in order of the number of site points, must satisfy this threshold. Normally, this setting is not relevant when a molecule or entry is used to restrict the search region. However, SiteMap could find more than a single site even in this case if the region is large or contains subsites that SiteMap is unable to combine into a single site.

- Report up to *n* sites—Enter the maximum number of sites to report, ranked in order of decreasing size (number of site points). The default for this setting is to report up to the 5 largest sites found in the initial site-finding stage. This setting is not active when a ligand or other species is used to restrict the size and location of the mapping region.
- Use *type* definition of hydrophobicity—Choose the definition of hydrophobicity to use in the calculation. The choices are labeled more restrictive and less restrictive. The less restrictive definition corresponds closely to the definition used in the original version of SiteMap. The more restrictive definition eliminates points that are adjacent to defined hydrophilic regions and assigns reduced hydrophobicity to solvent-exposed regions.[1] See Section 3.2.2 on page 31 for more information. The more restrictive definition is the default choice.
- Use *type* grid—Choose the size of the grid to use in computing the displayed site maps. The choices are coarse, standard, and fine, corresponding to grid spacings of 1.0 Å, 0.7 Å, and 0.35 Å. The default is standard.

  It should be emphasized that the choice of grid increment has no effect on the site-finding or site-evaluation stages of the algorithm, which always position the site points on a 1-Å grid.
- Crop SiteMaps at *n* Å from nearest site point—Enter the distance from the nearest site point at which to crop the individual site maps for display in Maestro. The default is 4 Å. No data is lost when the map is cropped. This option merely affects the truncation of the displayed surface, and the distance can be altered during the Maestro session.
- Use the *type* force field—Choose the variant of the OPLS-AA force field to be used. The default is OPLS_2005; the alternative is OPLS_2001.

4.1.4 Job Incorporation

When a SiteMap job finishes, the site points and site maps are automatically incorporated into the current Maestro project, and associated with the receptor. The incorporation is done by reading and executing the *jobname*`.cmd` file written by SiteMap. This process opens and closes Maestro panels in rapid succession. On some operating systems, you can use `Xvfb` (X Virtual Frame Buffer[2]) to suppress the opening and closing of panels while the results are incorporated. To do so you must set the environment variable `SCHRODINGER_USE_XVFB` (to any non-null value) prior to starting Maestro. In this mode, the SiteMap executable uses the command file to silently create a Maestro project. When the project appears to be complete, Maestro

1. This definition favors enclosed phobic regions, like the Glide XP definition of hydrophobic enclosure. However, SiteMap's definition is not as restrictive as is the Glide XP definition, which has geometric elements that need not be met by the SiteMap definition.
2. Please see the notice regarding third party programs and third party Web sites on the copyright page at the front of this manual.

merges it into the current Maestro project. Information on the `Xvfb` executable is given in Appendix A.

By default, files that are not needed for incorporation into Maestro are removed. However, the file cleanup (and the SiteMap job) is aborted if a problem is found with an Impact job step, so that the log file is available for inspection.

4.1.5 Viewing the Results

When the results are incorporated, the Surface Table panel is opened. You can use the controls in this panel to change the display attributes of the various maps. The accptr, donor, and phob maps are displayed by default; the phil and surf maps are not displayed by default.

The default appearance of the six map types is as follows:

- Hydrophobic map—yellow mesh
- Hydrophilic map—green mesh
- Hydrogen-bond donor map—blue mesh
- Hydrogen-bond acceptor map—red mesh
- Metal-binding map—pink mesh
- Surface map—gray surface, 50% transparency

Thus, a red ligand oxygen atom that accepts a hydrogen bond from the receptor or coordinates with a metal center should appear in a red acceptor or pink metal-binding region, and a polar hydrogen on a blue amide nitrogen should appear in a blue donor region. (Red and blue are the default colors for oxygen and nitrogen.)

You can change the cropping of any of the maps with the following procedure:

1. Select the map in the table.
2. Click Limit.
3. In the Limit dialog box, select Molecule from the Pick menu.
4. Pick a site point.
5. Enter the new distance in the Distance text box.
6. Click OK.

Note: Do not change the molecular representation. Changing representations affects the display of the site points, and cannot be reversed without restarting Maestro.

You can change the value at which the maps are contoured (the isovalue), as follows:

1. Display the desired map, and undisplay all the others.
2. Adjust the Isovalue slider, or enter a value in the adjacent text box.

The other display properties of these surfaces, such as color or representation can also be changed. For more information, see Section 11.4 of the *Maestro User Manual*.

4.2 Sample Site Maps

To illustrate a typical application, Figure 4.3 and Figure 4.4 show the co-crystallized ligand for the thrombin 1ett receptor and the generated site points (white) in the context of the receptor structure and of the gray, translucent SiteMap surface. Figure 4.3 focuses on relatively exposed regions of the site, while Figure 4.4 profiles the buried specificity pocket. Figure 4.5 and Figure 4.6, taken from the same viewpoints, display the hydrophobic (yellow) and the hydrogen-bond donor (blue) and acceptor (red) maps, but for clarity suppress the receptor surface. The hydrophobic groups on the ligand can clearly be seen occupying hydrophobic regions, and the donors and acceptors of the ligand are located in or very close to the appropriate donor and acceptor regions.

4.3 Running SiteMap from the Command Line

SiteMap can be run from the command line with the `sitemap` command. When the calculation finishes, the job can create a Maestro project, and start a Maestro session to display the site maps, if requested. The syntax of the `sitemap` command is as follows:

```
$SCHRODINGER/sitemap [options] -j jobname -prot file.mae
$SCHRODINGER/sitemap [options] -proj name [-j jobname] -prot file.mae
```

The principal arguments are described below.

`-proj` *projname*	Create a Maestro project with the given name, containing the protein, the ligand (if given), the sites, their SiteMaps, and their properties, and start Maestro with this project loaded. When this argument is not used, the calculation stops with generation of a command file, *jobname*.cmd, that can later be read into Maestro. *projname* can be given with or without the `.prj` suffix.
`-j` *jobname*	Specify the job name. *jobname* is used to make some file names unique. Required if `-proj` is not given. If `-proj` is given and `-j` is not, the project name (omitting the `.prj`) is used for the job name.
`-prot` *file*`.mae`	Specify protein file in Maestro format. Required.

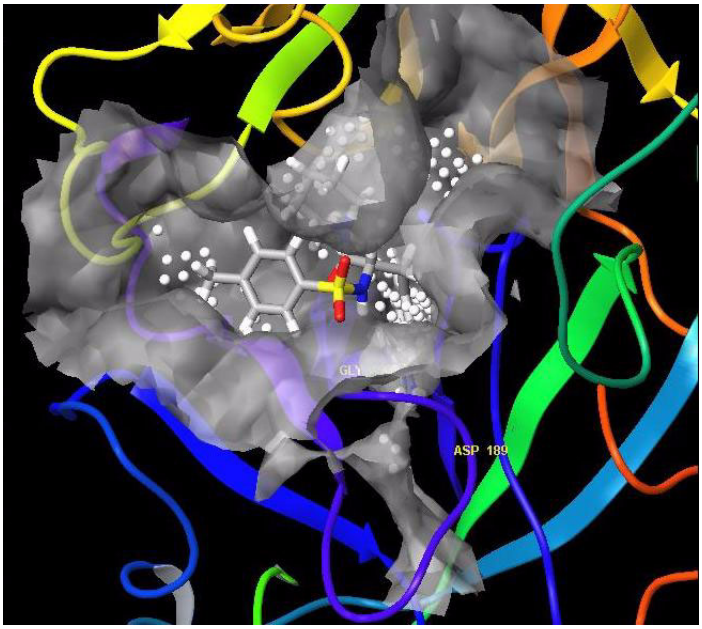

Figure 4.3. SiteMap surface and site points for 1ett, exterior of pocket

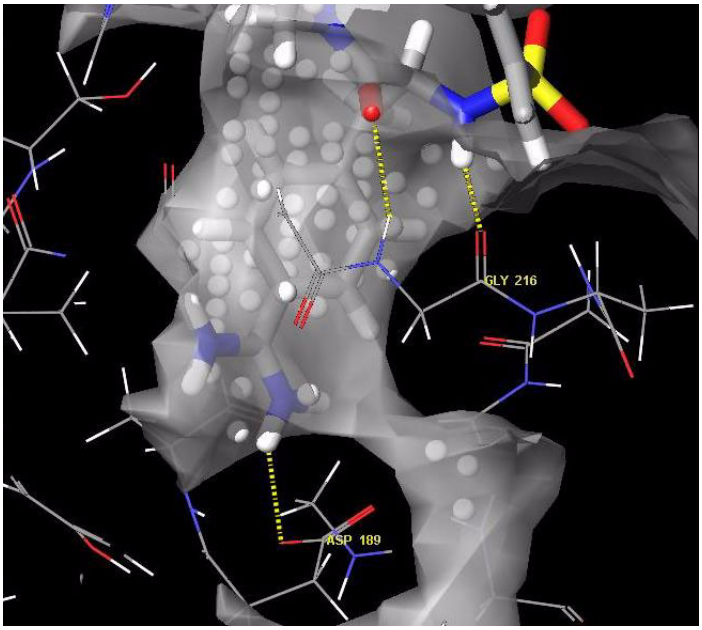

Figure 4.4. SiteMap surface and site points for 1ett, inside pocket

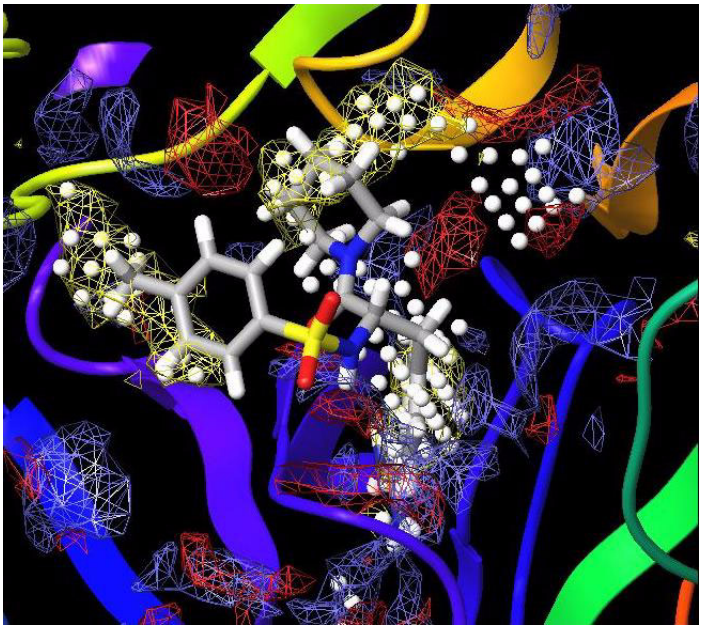

Figure 4.5. Hydrophobic, donor, and acceptor maps for 1ett, exterior of pocket

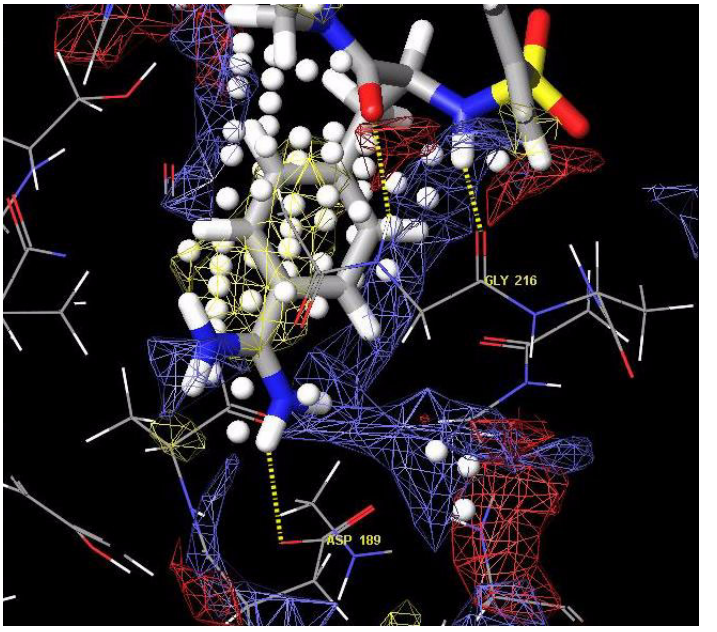

Figure 4.6. Hydrophobic, donor, and acceptor maps for 1ett, inside pocket

4.3.1 Command Options

The options for the `sitemap` command are given in Table 4.1. These options are classified into the common options, additional options, and advanced options. The common options include the ones that are set from the SiteMap panel in Maestro. The `sitemap` command also accepts some standard Job Control options, which are listed in Table 4.2.

Table 4.1. Options for the sitemap command.

Option	Description
`-xvfb { yes | no }`	Use the X Virtual Frame Buffer process to silently create a Maestro project. Requires that `-proj` is specified and that `Xvfb` is in your `PATH`. See for information on obtaining `Xvfb`.
`-ligmae` *filename* `-ligsdf` *filename*	Include optional ligand file in Maestro or SD format.
`-sitebox` *dist*	If an optional ligand file is specified, restrict the site-finding step to a box placed around the ligand plus a margin of *dist*.
`-reportsize` *size*	Minimum number of site points per reported site group in the first stage. The final number of site points may include extension points if `-extend` is used with a positive value or `-addsp yes` is given. Default: 15.
`-maxsites` *n*	Number of sites to report. Default: 5
`-modphobic` *n*	Definition to be used for hydrophobic regions. Default: 3. Allowed values are: 0: Use the least restrictive definition, which is the original definition 1: Exclude site points that are exposed, close to hydrophilic regions, or too close to the protein 2: Scale phobic potential by exposure fraction 3: Exclude points and scale potential.
`-grid` *gridsize*	Grid size (Å) to be used in the mapping calculations. Default: 0.7, corresponding to `-resolution standard`.
`-resolution` *res*	Alternative means for specifying the grid size. Allowed values of *res* are `low` for 1.0 Å, `standard` for 0.7 Å or `high` for 0.35 Å.
`-mapdist` *dist*	Restrict displayed SiteMaps to *dist* from the nearest site point. Default: 4 Å. Can be overridden, up to the *margin* distance, by using the Limit facility in the Surface Table panel.
`-ffield` *version*	Version of OPLS force field to use. Allowed values are `OPLS_2001` and `OPLS_2005`. Default: `OPLS_2005`.
`-extend` *intdist*	When evaluating exposure in the site-evaluation stage, try adding "extension" site points at grid points up to *intdist* from the existing site points. Default: 3 Å.

Table 4.1. Options for the sitemap command. (Continued)

Option	Description
`-addsp { yes | no }`	Add "extension" site points to the site-point set if they fall in regions that satisfy the threshold criteria for phobicity or philicity. Default: `yes`.
`-cleanup { yes | no }`	Remove all files not needed for the Maestro session. The file cleanup (and the SiteMap job) is aborted if a problem is found with an Impact job step, so that the log file is available for inspection. Default: `yes`.
`-keepeval { yes | no }`	Keep the evaluation-step log files even if `-cleanup yes` is given. This option, together with `-keepmaestro no`, can be used to obtain just the SiteScore and the SiteMap properties, which are listed at the end of the log files, while removing other files. Default: `no`.
`-keeplogs { yes | no }`	Keep the log files from all stages even if `-cleanup yes` is given. Sets or resets `keepeval` to `yes`. This option is set to yes if the value of the `-verbosity` option is greater than 1. Default: `no`.
`-keepmaestro { yes | no }`	Keep or remove Maestro-specific files. If `-proj` and `-cleanup yes` are given, the default is to remove the Maestro-specific files if the session is successfully loaded; `-keepmaestro yes` keeps them. If the project is not successfully loaded, or if `-proj` is not given, the default is to keep the files; `-keepmaestro no` deletes them
Additional options	
`-cmdfile` *filename*	Name for the Maestro command file. Default: *jobname*`.cmd`
`-enclosure` *fraction*	Fraction of ray directions from a grid point that must intersect the protein within a specified distance for that grid point to be considered as a potential site point. Default: 0.5.
`-maxdist` *dist*	Distance within which a directional ray from a candidate grid point must intersect the protein surface. Default: 8 Å.
`-maxvdw` *vdw-energy*	Maximum van der Waals interaction energy (kcal/mol) for a grid point to be excluded as a potential site point. This quantity is the negative of the computed interaction energy, so the argument supplied must be positive. Default: 1.1.
`-verbosity <0|1|2|3>`	Control level of detail in output log files. Default: 0.
`-margin` *margin*	Grid-box margin (Å) to be used in the SiteMap calculations. Default: 6 Å.
`-addphob` *thresh*	Threshold for adding phobic points. Default: –0.50 if `-modphobic` option is 2 or 3, otherwise –0.75.
`-addphil` *thresh*	Threshold for adding philic points. Default: –8 kcal/mol
`-overwrite { yes | no }`	Bypass prompt for instructions if the project directory already exists and delete (overwrite) the existing project directory. Default: `no`.

Table 4.1. Options for the sitemap command. (Continued)

Option	Description
`-loadtime` *maxtime*	Maximum time in seconds allowed for successful initialization and loading of the Maestro session from the `.cmd` file. If the session is not successfully loaded within this time interval, the Maestro-specific files are kept (overrides `-keepmaestro no`). If *maxtime* ≤ 0, a Maestro session is not started and the Maestro files are kept unless `-keepmaestro no` is specified. Default: 60 sec.
`-h`	Print brief usage summary.
`-help`	Print full usage summary.
Advanced options	
`-dvscale` *ratio*	Squared distance ratio for determining whether a site point is inside or outside the protein. A site point is outside the protein if the ratio of the square of the protein-atom/site point distance to the protein-atom van der Waals radius is larger than this value for all protein atoms. Default: 2.5 $Å^2$.
`-nthresh` *n*	Minimum number of candidate site-point neighbors required to be within a given distance for a candidate site point to be eligible for inclusion in a site-point group. The square of the distance is specified by `-dthresh`. Default: 3.
`-d2thresh` *value*	Squared distance used in `-nthresh` test. Default: 3.1 $Å^2$.
`-kmax` *n*	Maximum sum of differences in grid indices to nearest site point allowed to add a candidate site point to a site-point group. Default: 3.
`-kmax2` *n*	Maximum sum of squares of differences in grid indices to nearest site point allowed for a candidate site point to be added to a site-point group Default: 5.
`-mingroup` *n*	Minimum number of points in a site-point group required to constitute a site. Default: 3.
`-dthresh` *value*	Threshold for the minimum distance separating site points in two site-point groups for them to be considered for merging into a single group. If the minimum distance is larger than this value, the groups will not be merged. Default: 6.5 Å.
`-rthresh` *value*	Threshold for the ratio of the distance between the centroids of two site-point groups to the effective sizes of the groups for groups to be considered for merging. Default: 5.

Table 4.1. Options for the sitemap command. (Continued)

Option	Description
`-r2thresh` *value*	Threshold for determining whether two site-point groups being considered for merging have successfully been interconnected by solvent-exposed bridging points. The squared distance from a bridging point between the groups to any site point must be less than *value* for the groups to be merged. Default: 4.1 Å^2.
`-cutoff` *cutdist*	Restrict the calculation of van der Waals and electrostatic potentials to protein atoms that lie within *cutdist* angstroms of a grid point.. Default: 20 Å.
`-modvdw { yes | no }`	Adjust van der Waals radii to improve the accuracy with which preferred locations of hydrogen donors and heavy-atom acceptors are represented in the site maps. Default: `yes`.
`-modcharges { yes | no }`	Scale down formal-charge contributions to the protein partial atomic charges by 50%. Default: `yes`.

Table 4.2. Standard Job Control options recognized by the sitemap command

Option	Description
`-LOCAL`	Run job in current working directory.
`-HOST` *hostname*	Submit job to host *hostname*. If this option is omitted, the job is run on the local host.

4.3.2 SiteMap Output

The following output is generated by SiteMap:

- Maestro command file. This file contains the commands necessary to import and display the SiteMaps. The default name of the command file is *jobname*`.cmd`.
- Site-point files (in Maestro format) and map files (`.vis` and `.grd`). These files are read by Maestro to display the SiteMaps. For each site, a set of five or six map files is produced, containing the hydrophobic, hydrophilic, donor, acceptor, surface, and metal-binding maps.
- A Maestro project, if `-proj` is given with the `sitemap` command.
- Log files. These are removed by default when the job finishes successfully. The options `-keeplogs` and `-keepeval` can be used to control which log files are kept.

4.3.3 Viewing Site Maps

If you use the `-proj` option to specify a project with the `sitemap` command, a Maestro project is created, and Maestro is automatically started, loading the project and displaying the site maps.

If you do not supply a project name with the `sitemap` command, the site maps are not automatically loaded into Maestro and displayed. To view the site maps in an existing Maestro session, use the following instructions:

1. From the Edit menu in the main window, choose Command Script Editor.

   The Command Script Editor panel opens.

2. Click Open Local.

   A file selector labeled Open Local Script Files opens.

3. Navigate to *jobname*`.cmd`, select it and click Open.

   The file selector is dismissed, and the Run Script button in the Command Script Editor panel becomes available.

4. Click Run Script.

   The script opens and closes the necessary panels to import all the files, and display the site maps.

To start a new Maestro session to view the site maps, use the following command:

```
$SCHRODINGER/maestro -c jobname.cmd
```

4.4 Adapting SiteMap

SiteMap provides control over many aspects of the calculations through command-line options, so that you can adapt SiteMap to the systems that you are interested in. The following subsections describe a number of different scenarios with the relevant command options.

4.4.1 Adjusting the Closeness of the Map to the Protein

The `-dvscale` option can be used to increase or decrease the number of grid points that lie outside the protein. The default value of 2.5 already allows fairly close approach to the protein. A value of 4 corresponds to the minimum-energy van der Waals distance for a homonuclear contact.

4.4.2 Tailoring the Definition of Hydrophobicity

Four `-modphobic` options are provided to tailor the definition of phobicity. Of these, Maestro employs the `-modphobic 3` ("more restrictive") and `-modphobic 0` ("less restrictive") options. It should be noted that the phobic-property score is calibrated such that the average phobic score and the average SiteScore for the previously discussed tight-binding complexes are 1.0, whichever phobic option is chosen. Thus, while the size and shape, and sometimes location, of displayed phobic regions will depend on the option selected, the average contribution of phobicity to the overall SiteScore for the tight-binding sites does not. What happens is that phobicity becomes more important for some binding sites and less important for others as the definition changes.

4.4.3 Finding Shallow Sites

If you are interested in finding relatively shallow sites, you can use the `-enclosure`, `-maxdist`, and `-maxvdw` options to make the site-finding step more receptive to finding relatively shallow sites. In particular, additional site-point positions will be recognized as valid candidates for inclusion in a site if some combination of the following is done:

- Make the threshold on the van der Waals energy for accepting points, set with `-maxvdw`, smaller than the default value of 1.1 kcal/mol.
- Make the maximum distance from a point to the protein, set with `-maxdist`, greater than the default value of 8 Å.
- Make the enclosure fraction, set with `-enclosure`, smaller than the default of 0.5.

You may need to explore these modifications of the default parameters to find sites appropriate for protein-protein interactions, for example.

4.4.4 Obtaining Only the SiteMap Properties

If you only want the values of the Maestro properties from the SiteMap calculation and not the maps, you can use the options `-keepeval yes` and `-keepmaestro no`. The latter option deletes the files used for the Maestro session. The Maestro properties are listed in the final lines of the evaluation-step log files. You should also ensure that you do not use the `-proj` option to specify a Maestro project.

4.4.5 Specifying a Reference Ligand Without Restricting the Mapping Region

If a molecule or entry is used to restrict the mapping box, Maestro sets both the `-ligmae` and `-sitebox` options. From the command line, you can use `-ligmae` (or `-ligsdf`) without

using `-sitebox` to specify a species that is to serve as a positional reference without restricting the region to be mapped. The refdist and refmin properties are generated in this case. This approach makes it easy to determine which receptor site, if any, corresponds to the reference site.

4.4.6 Controlling the Merging of Sites

You can control how sites are merged when they are separated by a short distance that could plausibly be bridged by a ligand in a solvent-exposed region. There are two measures of how close two groups must be to be considered for merging: the distance between the nearest site points in the two groups, and the ratio of the distance between the centroids of the groups to their effective size. The threshold for the first is set by `-dthresh`, and the threshold for the second is set by `-rthresh`. Both must be satisfied.

In addition to these two measures, there is a measure of whether two site-point groups being considered for merging have successfully been interconnected by solvent-exposed bridging points. The threshold for this measure is set by `-r2thresh`. When two groups are considered for merging, a bridging point is "grown" from one group. If it is sufficiently close to the nearest point in the other group, the groups are merged. The threshold is the minimum squared distance between the bridging point and the nearest point in the second group.

SiteMap Results

To calibrate and characterize the SiteMap properties, SiteMap has been applied to an extensive set of 230 proteins, which were taken either from the Glide database-enrichment suite or from the PDBbind database [5]. These proteins bind ligands of molecular weight at least 150 with affinities of at least 100 µM. Of the 230 proteins, 155 have binding affinities of 1 µM or less. The proteins were prepared using standard Schrödinger techniques. To avoid prejudicing the search, all crystallographic water was removed.

The entire data set was used to optimize the contributions to the overall SiteScore of the SiteMap properties described in Section 3.3. The criterion for the optimization was that the site with the best SiteScore corresponded to the co-crystallized site as often as possible. The tight-binding set was further used to calibrate SiteScore and its contact, phobic, and philic components so that the average value for each of these quantities is 1.0. The most significant terms are the size of the site as measured by the number of site points, the relative openness of the site as measured by the exposure and enclosure properties, and the tightness of the site as measured by the contact property. The phobicity of the site plays a smaller role, and the site philicity plays a small enough role that it could have been excluded.

Table 5.1 summarizes SiteMap's accuracy in locating the primary (co-crystallized) binding site for the 230 proteins and for the 155 submicromolar binders. As Nayal and Honig [1] find for Screen and report for other methods, size is a fairly good predictor of the ligand-binding site. However, SiteScore is a better predictor, correctly locating the primary binding site in 96.5% of the proteins in the full set and 98.1% in the tight-binding set.

Table 5.1. Performance in Locating the Primary Binding Site in Proteins

	230 Proteins		155 Tight Binders	
Comparison	**Number**	**Percent**	**Number**	**Percent**
Primary site not found	0	0.0	0	0.0
Largest site scores best	203	88.3	139	89.7
Largest site is correct	201	87.4	139	89.7
Best-scoring site is correct	222	96.5	152	98.1
Largest or best-scoring site is correct	224	97.4	153	98.7

SiteMap can also be employed as a "classifier" to discriminate sites that bind ligands from sites that don't. The objective is to determine whether a protein is likely to bind ligands tightly, not to decide which site in the protein to target. SiteMap can be used in this way by setting a threshold SiteScore value for recognition as a drug-binding site of 0.80 (80% of the average found for the 155 submicromolar sites). Used as a classifier, SiteMap performs as shown in Table 5.2. Similar results for the percentage of primary binding sites correctly classified (true positives) were reported for a different set of proteins by Nayal and Honig [1].

Table 5.2. Performance of SiteScore Threshold in Classifying Primary Binding Sites in Proteins

	230 Proteins		155 Tight Binders	
Comparison	**Number**	**Percent**	**Number**	**Percent**
Primary site not found	0	0.0	0	0.0
Primary site incorrectly classified	24	10.4	15	9.7
Primary site correctly classified	206	89.6	140	90.3

Getting Help

Schrödinger software is distributed with documentation in PDF format. If the documentation is not installed in `$SCHRODINGER/docs` on a computer that you have access to, you should install it or ask your system administrator to install it.

For help installing and setting up licenses for Schrödinger software and installing documentation, see the *Installation Guide*. For information on running jobs, see the *Job Control Guide*

Maestro has automatic, context-sensitive help (Auto-Help and Balloon Help, or tooltips), and an online help system. To get help, follow the steps below.

- Check the Auto-Help text box, which is located at the foot of the main window. If help is available for the task you are performing, it is automatically displayed there. Auto-Help contains a single line of information. For more detailed information, use the online help.
- If you want information about a GUI element, such as a button or option, there may be Balloon Help for the item. Pause the cursor over the element. If the Balloon Help does not appear, check that Show Balloon Help is selected in the Help menu of the main window. If there is Balloon Help for the element, it appears within a few seconds.
- For information about a panel or the folder that is displayed in a panel, click the Help button in the panel. The Help panel is opened and a relevant help topic is displayed.
- For other information in the online help, open the Help panel and locate the topic by searching or by category. You can open the Help panel by choosing Help from the Help menu on the main menu bar or by pressing CTRL+H.

  To view a list of all available SiteMap–related help topics, click the Categories tab, then from the Categories menu, choose SiteMap. Double-click a topic title to view the topic.

If you do not find the information you need in the Maestro help system, check the following sources:

- *Maestro User Manual*, for detailed information on using Maestro
- *Maestro Command Reference Manual*, for information on Maestro commands
- Frequently Asked Questions pages on the Schrödinger Support Center

The manuals are also available in PDF format from the Schrödinger Support Center. Information on additions and corrections to the manuals is available from this web page.

If you have questions that are not answered from any of the above sources, contact Schrödinger using the information below.

E-mail: help@schrodinger.com
USPS: Schrödinger, 101 SW Main Street, Suite 1300, Portland, OR 97204
Phone: (503) 299-1150
Fax: (503) 299-4532
WWW: http://www.schrodinger.com
FTP: ftp://ftp.schrodinger.com

Generally, e-mail correspondence is best because you can send machine output, if necessary. When sending e-mail messages, please include the following information, most of which can be obtained by entering `$SCHRODINGER/machid` at a command prompt:

- All relevant user input and machine output
- SiteMap purchaser (company, research institution, or individual)
- Primary SiteMap user
- Computer platform type
- Operating system with version number
- SiteMap version number
- Maestro version number
- mmshare version number

Obtaining and Using Xvfb

SiteMap creates a Maestro project by starting a Maestro session and running a Maestro command file. The commands open and close various Maestro panels, which can be visually undesirable. To avoid this problem you can install `Xvfb` (X Virtual Frame Buffer), if your machine has a supported UNIX or Linux operating system. This program prevents the display of the Maestro panels.

The latest version of `Xvfb` for some UNIX and Linux operating systems can be obtained from one of the following links[3]:

ftp://ftp.xfree86.org/pub/XFree86/4.5.0/binaries

http://ftp.xfree86.org/pub/XFree86/4.5.0/binaries

The link displays a number of folders that contain `.tgz` files for various XFree86 executables, including a file named `Xvfb.tgz`. For Linux, for example, five `Linux-ix86-`*lib* folders are available, where *lib* is `glibc20`, `glibc21`, `glibc22`, `glibc23`, or `libc5`. To determine the correct Linux version for your hardware, run the command:

```
rpm -qi libc
```

A version number like 2.2.5 means that the `glibc22` version is required. Download, unzip, and untar the appropriate `Xvfb.tgz` file to obtain the `Xvfb` executable, then place it in an appropriate directory. Make sure that this directory is included in your `PATH` environment variable.

3. Please see the notice regarding third party programs and third party Web sites on the copyright page at the front of this manual.

References

1. Nayal, M.; Honig, B. On the nature of cavities on protein surfaces: Application to the identification of drug-binding sites. *Proteins* **2006**, in press.

2. Friesner, R. A., Murphy, R. B., Repasky, M. P., Frye, L. L., Greenwood, J. R., Halgren, T. A., Sanschagrin, P. C., Mainz, D. T. Extra Precision Glide: Docking and Scoring Based on a New Theory of Molecular Recognition. *J. Med. Chem.* (submitted).

3. Weber, A.; Halgren, T. A. et al. Design and Synthesis of P2-P1'-Linked Macrocyclic Human Renin Inhibitors. *J. Med. Chem.* **1991**, *34*, 2692.

4. Goodford, P. J. A Computational Procedure for Determining Energetically Favorable Binding Sites on Biologically Important Macromolecules. *J. Med. Chem.* **1985**, *28*, 849.

5. Wang, R.; Fang, X.; Lu, Y.; Yang, C.-Y.; Wang, S. The PDBbind Database: Methodologies and updates. *J. Med. Chem.* **2005**, *48*, 4111.

6. Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shelley, M.; Perry, J. K.; Shaw, D. E.; Francis, P.; Shenkin, P. S. Glide: A New Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking Accuracy. *J. Med. Chem.* **2004**, *47*, 1739.

Copyright Notices

NCSA HDF5 Software Library and Utilities

Copyright Notice and Statement for NCSA HDF5 (Hierarchical Data Format 5) Software Library and Utilities

Contributors: National Center for Supercomputing Applications (NCSA) at the University of Illinois at Urbana-Champaign (UIUC), Lawrence Livermore National Laboratory (LLNL), Sandia National Laboratories (SNL), Los Alamos National Laboratory (LANL), Jean-loup Gailly and Mark Adler (gzip library).

Redistribution and use in source and binary forms, with or without modification, are permitted for any purpose (including commercial purposes) provided that the following conditions are met:

1. Redistributions of source code must retain the above copyright notice, this list of conditions, and the following disclaimer.
2. Redistributions in binary form must reproduce the above copyright notice, this list of conditions, and the following disclaimer in the documentation and/or materials provided with the distribution.
3. In addition, redistributions of modified forms of the source or binary code must carry prominent notices stating that the original code was changed and the date of the change.
4. All publications or advertising materials mentioning features or use of this software are asked, but not required, to acknowledge that it was developed by the National Center for Supercomputing Applications at the University of Illinois at Urbana-Champaign and to credit the contributors.
5. Neither the name of the University nor the names of the Contributors may be used to endorse or promote products derived from this software without specific prior written permission from the University or the Contributors, as appropriate for the name(s) to be used.

6. THIS SOFTWARE IS PROVIDED BY THE UNIVERSITY AND THE CONTRIBUTORS "AS IS" WITH NO WARRANTY OF ANY KIND, EITHER EXPRESSED OR IMPLIED. In no event shall the University or the Contributors be liable for any damages suffered by the users arising out of the use of this software, even if advised of the possibility of such damage.

Portions of HDF5 were developed with support from the University of California, Lawrence Livermore National Laboratory (UC LLNL). The following statement applies to those portions of the product and must be retained in any redistribution of source code, binaries, documentation, and/or accompanying materials:

This work was partially produced at the University of California, Lawrence Livermore National Laboratory (UC LLNL) under contract no. W-7405-ENG-48 (Contract 48) between the U.S. Department of Energy (DOE) and The Regents of the University of California (University) for the operation of UC LLNL.

DISCLAIMER: This work was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor the University of California nor any of their employees, makes any warranty, express or implied, or assumes any liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately-owned rights. Reference herein to any specific commercial products, process, or service by trade name, trademark, manufacturer, or otherwise, does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or the University of California. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or the University of California, and shall not be used for advertising or product endorsement purposes.

C and C++ Libraries for Parsing PDB Records

The C and C++ libraries for parsing PDB records are Copyright (C) 1989 The Regents of the University of California. All rights reserved.

Redistribution and use in source and binary forms are permitted provided that the above copyright notice and this paragraph are duplicated in all such forms and that any documentation, advertising materials, and other materials related to such distribution and use acknowledge that the software was developed by the University of California, San Francisco. The name of the University may not be used to endorse or promote products derived from this software without specific prior written permission. THIS SOFTWARE IS PROVIDED "AS IS" AND WITHOUT ANY EXPRESS OR IMPLIED WARRANTIES, INCLUDING, WITHOUT LIMITATION, THE IMPLIED WARRANTIES OF MERCHANTIBILITY AND FITNESS FOR A PARTICULAR PURPOSE.

120 West 45th Street
32nd Floor
New York, NY 10036

101 SW Main Street
Suite 1300
Portland, OR 97204

3655 Nobel Drive
Suite 430
San Diego, CA 92122

Dynamostraße 13
68165 Mannheim
Germany

QuatroHouse, Frimley Road
Camberley GU16 7ER
United Kingdom

SCHRÖDINGER.